Scientific Abstract

Approximately 130,000 new cases of colorectal carcinoma are diagnosed in the United States each year (Jessup et al., 1997). Nearly half of all patients with colorectal cancer will develop metastatic disease during the course of their illness (Meta-analysis Group, 1998). Fifteen percent of patients will have liver metastases at the time of diagnosis, and fully 60% of patients with metastatic disease will have liver-only or liver-predominant disease (Kemeny et al., 1994). Surgical resection can offer a subgroup (one third) of these patients an opportunity for cure; however, the majority have unresectable lesions or lesion recurrence following resection and consequently have few treatment options (Fong et al., 1995). Systemic chemotherapy yields responses in only 15%-35% of these patients, and radiotherapy is generally ineffective. Infusion of fluorinated pyrimidines (FUDR) into the liver has resulted in higher local response rates (40%-60%) without a convincing improvement in overall survival. Median time to disease progression remains 6 to 9 months, while overall survival in these patients ranges from 12 to 18 months (O'Connell et al., 1998).

MediGene, Inc. is currently evaluating an oncolytic virus, NV1020, as a potential new therapy for patients with colorectal cancer that has metastasized to the liver. NV1020 is a replication-competent herpes simplex type-1 virus (HSV-1) with an HSV-2 glycoprotein (gG) insertion that was genetically engineered to attenuate its pathogenic ability. The virulence of NV1020 is highly attenuated relative to the parental strain, HSV-1 (F) due to: (i) a deletion of 15 kb spanning the internal repeated region of the genome extending through UL56, and (ii) a 700-bp deletion that prevents expression of the UL24 gene. Deletion of the internal repeated region of HSV-1 has been strongly associated with loss of virulence, characterized by markedly higher LD_{50} values compared to wild-type virus when administered intracerebrally, loss of neuroinvasiveness, impaired replication in cornea and brain, and impaired ability to establish a reactivatable latent infection (Jenkins et al., 1996, Meignier et al., 1988; Meignier et al., 1990). NV1020 also expresses an exogenous copy of the HSV-1 TK gene, and thus is sensitive to anti-viral drugs such as acyclovir. NV1020 was extensively tested in HSV-sensitive animal models prior to use in clinical trials.

MediGene is currently conducting study NR1-001 entitled, "A Phase I Open-Label, Dose-Escalating Study of the Safety, Tolerability and Anti-Tumor Activity of a Single Intra-hepatic Arterial Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver." Only subjects who are herpes simplex type-I antibody positive (HSV-1 seropositive) are eligible for study NR1-001, which to date has enrolled 10 subjects. Three subjects have been dosed in each of the following dose cohorts: 3×10^6, 1×10^7 pfu and 3×10^7 pfu of NV1020. One subject has been dosed in the fourth cohort at 1×10^8 pfu of NV1020, and

the study is ongoing. All doses have been well tolerated, and no NV1020-related serious adverse events have been reported to date.

MediGene, Inc. would like to continue to evaluate NV1020 as a potential therapy in subjects with adenocarcinoma of the colon with metastasis to the liver. The new study, protocol NR1-003, is entitled, "A Phase I, Open-Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-tumor Activity of a Single Intrahepatic Arterial Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Herpes Simplex Seronegative Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver." The study is designed to assess the safety and tolerability of NV1020, and to determine the Maximum Tolerated Dose (MTD) in herpes simplex type-I antibody negative (HSV-1 seronegative) subjects with adenocarcinoma of the colon with metastasis to the liver. Secondary study objectives include assessments of the anti-tumor activity, immunogenicity, viral shedding, HSV reactivation, clearance and ability to replicate in metastatic lesions of colon cancer.

Protocol NR1-003 includes a total of four dose-escalating cohorts (with an option to escalate one additional cohort) with three subjects at a fixed dose per cohort. Up to 28 subjects may be enrolled. Subjects will have a CT scan of the liver and a complete assessment of tumor status prior to receiving a single intrahepatic arterial injection of NV1020. The first cohort will receive 1×10^7 pfu of NV1020, which was shown to be safe in study NR1-001 and is 10-fold lower than the dose currently being evaluated in study NR1-001. Each subsequent cohort will receive doses escalating by half-logs as follows: 3×10^7, 1×10^8 and 3×10^8 with an option to increase to 1×10^9 pfu. Three to 10 days after the injection, subjects may undergo placement of an intrahepatic arterial infusion pump. At this time, they will also undergo incisional biopsy of metastatic liver lesions and normal liver tissue. If surgical placement of the intrahepatic arterial pump is not clinically indicated or if the center does not routinely utilize pumps for regional delivery of chemotherapy, the tumor biopsies will be image-guided. Up to four tissue sites will be biopsied under image-guidance. Tissue samples will be evaluated for the presence of NV1020 by immunohistochemistry and PCR. NV1020 clearance from the hepatic venous circulation will be evaluated by PCR and culture of serum samples obtained from the hepatic vein at various time-points up to 60 minutes after NV1020 infusion. Safety will be monitored throughout the study by scheduled clinical assessments to detect HSV infection, neurotoxicity, microthrombosis, other adverse events and laboratory monitoring of hematologic, renal, hepatic, immune and clotting function, and assessment of HSV viral shedding. Cytokines and CEA will be followed throughout the study to monitor immune response and tumor progression. Anti-tumor activity of NV1020 will be determined by serial radiologic assessments of liver tumor status (WHO Response Criteria) and disease, as well as Karnofsky Performance Status. After 3 months, subjects will be followed in a long-term study, NR1-004

References

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